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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,311	12/22/2004	Roland Martin	4239-64111-05	9128

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,311	MARTIN ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-10,12-14,16,17 and 19-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-10,12-14,16,17 and 19-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/08, 5/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 11/30/2007, including arguments/remarks and amended claims, was received on 2/22/2008 and has been entered into the record.

2. Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 are currently pending and are the subject of this office action.

Information Disclosure Statement

The information disclosure statements received on 2/22/2008 and 5/20/2008 have been fully considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Nakatani *et al* ("Nakatani"), Vincenti *et al* ("Vincenti") , Hayosh *et al* ("Hayosh"), Paty *et al* ("Paty") and Jacobs *et al* ("Jacobs"), as set forth on pages 4-7 of the office action mailed on 11/30/2007.

The claims of the instant invention are drawn to methods of treating multiple sclerosis comprising administration of a therapeutically effective amount of interferon-beta and a therapeutically effective amount of an antibody that specifically binds the interleukin-2 receptor. The claims are further drawn to administration of interferon-beta-1a and interferon-beta-1b, and an anti-interleukin-2 receptor antibody that is an anti-Tac (CD25) antibody, and specifically daclizumab. Nakatani, Vincenti, Hayosh, Paty and Jacbobs

Nakatani discloses a humanized monoclonal antibody that specifically binds the interleukin-2 receptor, B-B10 (column 1, lines 5-12), and- teaches that this antibody is useful for treatment of various

diseases, including multiple sclerosis (column 2, lines 22-37). Nakatani is silent regarding treatment of multiple sclerosis by co-administration of this antibody with interferon-beta.

Vincenti discloses a humanized monoclonal antibody, daclizumab, specific for the interleukin-2 receptor, which is useful for preventing T-cell-mediated transplant rejection (see abstract). Vincenti also teaches that administration of daclizumab is not associated with adverse side effects (see abstract and p. 163). Vincenti is silent regarding the use of daclizumab for treatment of multiple sclerosis.

Hayosh teaches that an antibody specific for the interleukin-2 receptor, OX 39, can inhibit transfer of experimental autoimmune encephalomyelitis (EAE), which is an art-recognized model of multiple sclerosis. Specifically, Hayosh describes inhibition of EAE development in healthy rats that had received spleen cells from rats with EAE cultured with myelin basic protein. This transfer of EAE pathology was inhibited when spleen cells from rats with EAE were cultured with myelin basic protein and OX 39, showing that this anti-interleukin-2 receptor antibody could prevent disease in a model for multiple sclerosi (see p. 3772, 1^{st}-2^{nd} columns and Table II). Based on these results, Hayosh suggests the use of anti-interleukin-2 receptor antibodies for in vivo treatment of multiple sclerosis (p. 3774, last paragraph). However, Hayosh is silent regarding the use of interferon-beta for treatment of multiple sclerosis.

Paty and Jacobs teach administration of IFN-β-1b and IFN-β-1a, respectively, to patients suffering from multiple sclerosis. The disclosures of both documents indicate that both IFN-β molecules are effective in treating multiple sclerosis. Paty describes IFN-β-1b-treated patients with decreased brain inflammation, as evidenced by decreases in the number of lesions detected by MRI (abstract, p. 664-665), while Jacobs teaches that IFN-β-1a-treated patients had significantly fewer exacerbations and a decreased number and volume of brain lesions as determined by MRI (abstract). Neither Paty nor Jacobs teach administration of an antibody specific for interleukin-2 receptor.

In the response received on 2/22/2008, the Applicants argue that the instant invention is not obvious in view of the cited combination. Specifically, the Applicants assert that there would be no incentive to combine Vincenti with the other cited art because Vincenti teaches administration of dacluzimab for treatment of transplant rejection, and is silent regarding treatment of multiple sclerosis, and thus provides no motivation to administer dacluzimab for treatment of any autoimmune disease. The Applicants also argue that the claimed methods are unpredictable with regards to the antibody employed. Nakatani and Hayosh teach the B-B10 and OX39 antibodies, but are silent regarding any other antibody, including dacluzimab. The Applicants note that the FDA considers each individual antibody to be

unique, and therefore one of ordinary skill in the art would view B-B10, OX39, and dacluzimab as unique antibodies.

The Applicants further argue that agents which are effective individually do not render obvious any combined use, and cite the disclosure of Bowman as an example. In this example, Bowman showed failure of treating renal failure with cyclosporine, azathioprine, and prednisone compared to treatment with cyclosporine and prednisone. Therefore, a combination of agents does not always ensure superior effects compared to the individual agents.

Finally, the Applicants argue that the art does not teach treatment of patients who have failed to respond to IFN-β therapy, and that the results of the instant invention were unexpected in view of the art. Specifically, the Applicants have submitted and affidavit by Dr. Alice Fong showing the results of a clinical study in which patients with multiple sclerosis were treated with (1) dacluzimab (2 mg/kg) and IFN-β; (2) dacluzimab (1 mg/kg) and IFN-β, and (3) placebo and IFN-β. In this study, the patients receiving combined dacluzimab and IFN-β exhibited 24% - 72% decreases in lesions compared to IFN-β alone. The Applicants assert that this decreased number of lesions observed after combined dacluzimab and IFN-β treatment would not have been predictable in view of the art, and therefore the claims cannot be obvious.

These arguments have been fully considered and are not persuasive. Regarding Applicants' arguments that there is no incentive to combine the teachings of Vincenti with the disclosures of the other cited art, it is noted that Vincenti teaches that an anti-IL-2R antibody, dacluzimab, is capable of treating a condition characterized by increased T cell reactivity against target organs/antigens. Hayosh teaches that multiple sclerosis is characterized by autoreactive T cells, and that activation of these T cells can be prevented by an antibody that interferes with IL-2 production (Hayosh - p. 3771, 2nd column), and also shows that antibodies specific for the IL-2R are useful for treatment of multiple sclerosis. Thus, one of ordinary skill in the art would suspect that the antibody of Vincenti is an anti-IL-2R receptor antibody capable of blocking IL-2/IL-2R interaction and thus be useful for treating multiple sclerosis. Similarly, Nakatani also teaches that anti-IL-2R antibodies can be used to treat multiple sclerosis. Based on the disclosures of Hayosh and Nakatani, one of ordinary skill in the art would thus be motivated to use the anti-IL-2R antibody dacluzimab to treat multiple sclerosis. Furthermore, although the antibodies can be considered unique in regards to FDA applications, the standards for obtaining a patent are different from that of obtaining FDA approval for a given compound. In the instant case, the antibodies of Nakatani, Vincenti, and Hayosh are all antibodies which recognize the same antigen (IL-2R) and in the absence of evidence to the contrary, mediate the same biological effect, namely that of inhibiting signaling via the

IL-2R or blocking binding of IL-2 to the IL-2R. Thus, from a point of view of a person of ordinary skill in the art, the antibodies would not necessarily be distinct because they would not be expected to significantly differ in terms of biological effects.

The Applicants also argue that it the individual use of IFN-β or anti-IL-2R antibodies for treatment of multiple sclerosis does not render obvious the combination of IFN-β and anti-IL-2R, and in support of this assertion the Applicants cite Bowman et al, which shows that "triple therapy" of renal failure exhibited undesirable effects and was not effective in treatment compared to "double therapy". However, the disclosure of Bowman is limited to treatment of renal failure, rather than an autoimmune disorder involving autoreactive T cells, wherein said treatment is via administered prednisone, cyclosporine, and azathrioprine rather than IFN-β and anti-IL-2R. In the instant case, both IFN-β and anti-IL-2R inhibit T cell function (see Hayosh, p. 3771, 2nd column and Jacobs, p. 292, last paragraph), and although anti-IL-2R and IFN-β mediate these effects via different mechanisms, a person of ordinary skill in the art would know that both treatments would result in inhibition of immune function. Therefore, one of ordinary skill in the art would have the motivation to combine anti-IL-2R antibodies and IFN-β because the skilled artisan would know that (1) both agents can act to suppress the immune system, and (2) both agents have been shown to be useful for treating multiple sclerosis.

In regards to Applicants' assertion that the instant invention provides unexpectedly superior results, it is noted that the 37 CFR 1.132 affidavit by Dr. Alice Fong shows that administration of combined dacluzimab and IFN-β resulted in a decreased percentage of neural lesions compared to IFN-β alone. The Applicants argue that this decrease in neural lesions after combined therapy would not have been predictable to one of skill in the art, and therefore the claims cannot be obvious. It is noted, however, that the art teaches that anti-IL-2R antibodies and IFN-b are, by themselves, useful for treatment of multiple sclerosis. The Fong affidavit describes combined anti-IL-2R and IFN-β therapy compared to only IFN-β. However, the study does not compare combined therapy to administration of IL-2R antibodies alone, and because anti-IL-2R administration has been shown to be useful for treatment of multiple sclerosis, one of ordinary skill in the art would not know if the results of the study detailed in the Fong affidavit were truly unexpected, or were the result of a beneficial effect of the anti-IL-2R antibody.

Finally, the Applicants have argued that the art does not suggest treatment of multiple sclerosis patients who have failed IFN-β therapy. However, because one of ordinary skill in the art would know, via Nakatani and Hayosh, that anti-IL-2R therapy would also be effective in treating multiple sclerosis, a skilled artisan would be motivated to supplement failed IFN-β therapy with administration of anti-IL2R antibodies.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 20 *remains rejected* on the grounds of non-statutory obviousness-type double patenting, as being unpatentable over claims 1-21 and 29-34 of co-pending Application 10/607,598, as set forth on pages 7-8 of the office action mailed on 11/30/2007.

In the response received on 2/22/2008, the Applicants argue that the scope of the '598 application is distinct from that of the instant application because the '598 application teaches treatment of multiple sclerosis in the absence of IFN-β, whereas the claims of the instant application require administration of IFN-b.

These arguments have been fully considered and are not persuasive. It is noted that both the '598 application and the instant application claim treatment of multiple sclerosis by administering an anti-IL-2R antibody. Although the '598 application is drawn to treatment of multiple sclerosis in the absence of IFN-β, the use of IFN-β for treatment of multiple sclerosis is well-known in the art. As set forth in the previous office action on pages 7-8, Paty and Jacobs teach that IFN-β is useful for treating multiple sclerosis. Thus, it would have been obvious to one of ordinary skill in the art, based on the teachings of Paty and Jacobs, and the disclosure of the '598 application, which teaches that multiple sclerosis can be treated by administering an anti-IL-2R antibody, to combine anti-IL-2R antibodies and IFN-β for treating multiple sclerosis, and therefore the subject matter of the instant application and the '598 application are not patentably distinct.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647